Management of diffusely infiltrating glioma in the elderly

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Abstract: PURPOSE OF REVIEW Genetic, epigenetic, and expression analyses have refined the traditional, histopathology-based classification of diffusely infiltrating gliomas. This review summarizes these trends and implications for elderly patients. RECENT FINDINGS The vast majority of diffusely infiltrating gliomas in elderly patients share an unfavorable molecular phenotype, that is, telomerase reverse transcriptase promoter mutation in the absence of isocitrate dehydrogenase (IDH) mutation and 1p/19q codeletion. Histopathologically, these are mostly astrocytic tumors and treatment is guided by the methylation status of the O6-methylguanine-DNA-methyltransferase (MGMT) promoter. 1p/19q codeletion indicates oligodendroglial histology and benefit from the addition of procarbazine, chlorethyl-cyclohexyl-nitroso-urea/lomustine, and vincristine polychemotherapy to radiotherapy. These tumors are almost exclusively associated with IDH mutations, but their molecular profile is rare in elderly patients. Two large phase III trials, RTOG 0825 and AVAglio, failed to demonstrate an overall survival benefit from antiangiogenic therapy with bevacizumab added to combined chemoradiotherapy (TMZ) in patients with newly diagnosed glioblastoma, but a trend toward improved survival with increasing age can be noted. Ongoing clinical trials in elderly patients with diffusely infiltrating glioma will clarify the role of combined chemoradiotherapy, and of bevacizumab or other antiangiogenic agents as an adjunct to radiotherapy. SUMMARY The choice of first-line therapy in elderly patients with diffusely infiltrating glioma is between postoperative hypofractionated radiotherapy and chemotherapy, guided by MGMT methylation in most patients.

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Genetic, epigenetic, and expression analyses have refined the traditional, histopathology-based classification of diffusely infiltrating gliomas. This review summarizes these trends and implications for elderly patients.

Recent findings
The vast majority of diffusely infiltrating gliomas in elderly patients share an unfavorable molecular phenotype, that is, telomerase reverse transcriptase promoter mutation in the absence of isocitrate dehydrogenase (*IDH*) mutation and 1p/19q codeletion. Histopathologically, these are mostly astrocytic tumors and treatment is guided by the methylation status of the O6-methylguanine-DNA-methyltransferase (*MGMT*) promoter. 1p/19q codeletion indicates oligodendroglial histology and benefit from the addition of procarbazine, chlorethyl-cyclohexyl-nitroso-urea/lomustine, and vincristine polychemotherapy to radiotherapy. These tumors are almost exclusively associated with *IDH* mutations, but their molecular profile is rare in elderly patients. Two large phase III trials, RTOG 0825 and AVAglio, failed to demonstrate an overall survival benefit from antiangiogenic therapy with bevacizumab added to combined chemoradiotherapy (TMZ) in patients with newly diagnosed glioblastoma, but a trend toward improved survival with increasing age can be noted. Ongoing clinical trials in elderly patients with diffusely infiltrating glioma will clarify the role of combined chemoradiotherapy, and of bevacizumab or other antiangiogenic agents as an adjunct to radiotherapy.

Summary
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Keywords
elderly, glioma, isocitrate dehydrogenase, O6-methylguanine-DNA-methyltransferase

INTRODUCTION

The current diagnosis of gliomas is based on histopathologic features according to the World Health Organization (WHO) classification of primary brain tumors [1]. Diffusely infiltrating gliomas are assigned to WHO grades II–IV and further classified based on their lineage differentiation as astrocytic or oligodendroglial. Assignment of WHO grade IV is confined to glioblastoma and its variants, which are characterized by mostly astrocytic differentiation, microvascular proliferation, and necrosis [1]. In elderly patients aged 65 years or older, glioblastoma (WHO grade IV) accounts for 83.8% of new diagnoses of diffusely infiltrating gliomas, followed by diffuse astrocytoma (7.5%, WHO grade II) and anaplastic astrocytoma (5.8%, WHO grade III) [2▪]. However, the prognostic significance of histopathological classification is limited in the elderly population. Among patients aged 65–74 years, 1-year survival rates are 36.9% [95% confidence interval (CI): 33.1–40.6] for diffuse astrocytoma, 33.2% (95% CI: 29.0–37.3) for anaplastic astrocytoma and 25.3% (95% CI: 24.3–26.3) for glioblastoma [2▪]. Consequently, watchful waiting strategies advocated for WHO grade II tumors in younger patients are not feasible in the elderly population [3,4].

Recently, progress in the molecular characterization of gliomas led to the identification of a panel of prognostic markers and a novel classification of

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KEY POINTS

- A novel prognostic classification of diffusely infiltrating gliomas has been suggested based on the presence of isocitrate dehydrogenase (*IDH*) mutation, chromosome1p/19q codeletion and telomerase reverse transcriptase *(TERT)* promoter mutations.
- Diffusely infiltrating gliomas in elderly patients are characterized by the least favorable combination of these markers, that is, *TERT* promoter mutation in the absence of *IDH* mutation and 1p/19q codeletion.
- The mainstay of treatment in elderly patients is maximum safe resection followed by chemotherapy or radiotherapy.
- *MGMT* promoter hypermethylation predicts response to alkylating chemotherapy in patients with newly diagnosed as well as recurrent glioblastoma.
- There is a trend for benefit from antiangiogenic treatment with bevacizumab with increasing age.

prognostic entities based on the occurrence of isocitrate dehydrogenase (*IDH*) 1 or 2 mutations, deletions of chromosome arms 1p/19q, and mutations in the promoter region of the gene encoding telomerase reverse transcriptase (*TERT*) [5▪▪–7▪▪]. First, co-occurrence of mutant *IDH* and 1p/19q deletions is usually accompanied by *TERT* promoter mutations [5▪▪–7▪▪] and almost exclusively confined to WHO grade II/III tumors with oligodendroglial histology [8▪,9]. These tumors are associated with the most favorable prognosis [5▪▪,10–12]. Second, *IDH* mutant, 1p/19q noncodeleted tumors do not usually have *TERT* mutations [5▪▪–7▪▪] and are characterized by tumor suppressor gene *TP53* mutations, often accompanied by mutations in the alpha thalassemia/mental retardation syndrome X-linked (*ATRX*) gene [8▪,9]. Histologically, these are mostly astrocytic tumors [8▪,9] and the prognosis is intermediate [5▪▪,10–12]. Third, *IDH* wild-type tumors are mostly astrocytic tumors with mutant *TERT* and lack 1p/19q deletions [6▪▪,7▪▪]. *IDH* wild-type tumors are associated with poor prognosis and comprise the majority of elderly patients with diffusely infiltrating glioma [13]. Integrated analyses of genetic, epigenetic, gene expression, and microRNA expression data complement evidence that diffuse gliomas in the elderly are genetically distinct from gliomas in younger patients [5▪▪,13–15]. However, these advances in classifying gliomas have not yet been integrated in population-based epidemiological studies.

The incidence of astrocytic diffusely infiltrating gliomas increases with age, whereas oligodendroglial tumors are rare in elderly patients (Table 1) [2▪]. Considering the constantly increasing life expectancy in most societies around the world, the number of elderly patients with diffusely infiltrating glioma will grow. Yet, only few randomized clinical trials in elderly patients have been completed [16–19]. The particular paucity of data available to guide the treatment of elderly patients with WHO grade II gliomas as well as the comparable prognosis and molecular similarities with WHO grade III/IV tumors may justify analogous treatment in most cases (Fig. 1).

Concerns to enroll elderly patients with diffuse glioma into clinical trials include higher morbidity, reduced treatment tolerability and impairment of quality of life due to toxicity. However, evidence from several trials demonstrated that treatment of elderly patients with glioblastoma yielded stable or improved quality of life until progression [16,17,20]. Treatment modalities for diffusely infiltrating glioma comprise the classical triad of cancer therapeutics, that is, surgery, radiotherapy, and chemotherapy, but further individualizing treatments by targeting the molecular mechanisms that drive the malignant phenotype in elderly patients will ultimately improve outcome.

BIOPSY OR SURGERY?

Microsurgical resection or diagnostic biopsy is required for establishing the histopathologic diagnosis and should precede any further treatment. The therapeutic value of microsurgical resection is under debate, because sufficiently powered randomized trials in the elderly are lacking. Although retrospective studies suggest that maximum safe resection improves survival compared with biopsy in patients with WHO grade II gliomas [3,21,22], elderly patients are generally underrepresented in these cohorts. However, accumulating evidence suggests that maximum safe resection improves survival in elderly patients with WHO grade III/IV gliomas: among 372 patients aged over 65 years that were treated for anaplastic astrocytoma or glioblastoma within the Neuroonkologische Arbeitsgemeinschaft (NOA)-08 trial, extent of resection was an independent prognostic factor in a prespecified survival model that controlled for age, O^6-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation, study treatment and histology [18]. In a case-control study including 80 patients over 65 years that were matched for age, Karnofsky Performance Score (KPS), tumor location and adjuvant therapies, an overall survival benefit for surgery versus biopsy (5.7 versus 4.0 months, $P = 0.02$) was apparent [23]. These results are further supported by a retrospective study in 142 patients with newly diagnosed

Table 1. Age-specific annual incidence of diffusely infiltrating gliomas (Central Brain Tumor Registry of the United States, statistical report 2007–2011) [2▪]

	WHO grade	Age at diagnosis							
		0–19	20–34	35–44	45–54	55–64	65–74	75–84	85+
Oligodendroglioma	II	0.05 (0.05–0.06)	0.31 (0.29–0.33)	0.47 (0.44–0.50)	0.42 (0.39–0.44)	0.32 (0.29–0.34)	0.22 (0.20–0.26)	0.20 (0.17–0.24)	0.10 (0.07–0.15)
Anaplastic oligodendroglioma	III	0.05 (0.05–0.06)	0.31 (0.29–0.33)	0.47 (0.44–0.50)	0.42 (0.39–0.44)	0.32 (0.29–0.34)	0.22 (0.20–0.26)	0.20 (0.17–0.24)	0.10 (0.07–0.15)
Diffuse astrocytoma	II	0.27 (0.26–0.29)	0.50 (0.48–0.53)	0.58 (0.55–0.61)	0.61 (0.57–0.64)	0.79 (0.75–0.83)	1.02 (0.96–1.08)	1.14 (1.06–1.23)	0.68 (0.59–0.79)
Anaplastic astrocytoma	III	0.09 (0.08–0.10)	0.28 (0.26–0.30)	0.39 (0.36–0.41)	0.46 (0.43–0.48)	0.65 (0.61–0.69)	0.90 (0.85–0.96)	0.92 (0.85–0.99)	0.39 (0.32–0.47)
Glioblastoma	IV	0.15 (0.14–0.17)	0.41 (0.39–0.43)	1.23 (1.18–1.28)	3.59 (3.51–3.67)	8.03 (7.90–8.16)	13.09 (12.87–13.31)	15.03 (14.74–15.34)	8.95 (9.60–9.32)

glioblastoma aged more than 65 years, among which resection versus biopsy was associated with prolonged survival (13.0 versus 4.0 months, $P < 0.001$) [24]. Finally, biopsy versus surgical resection was associated with inferior overall survival [hazard ratio (HR) 1.50 (95% CI 1.17–1.92)] in multivariate analyses of the Nordic trial ($N = 342$), which compared two different radiotherapy regimens and temozolomide (TMZ) in patients with newly diagnosed glioblastoma aged more than 60 years [19]. In contrast, one retrospective single center cohort study of 58 patients aged more than 80 years failed to demonstrate prolonged survival of a sub-group of 12 patients that underwent gross total resection, as compared with incomplete resection or biopsy [25], but the small sample size of this cohort longs for further evaluation of the value of extent of resection in this particularly old subgroup of patients.

RADIOTHERAPY OR CHEMOTHERAPY – OR BOTH?

The European Organization for Research and Treatment of Cancer (EORTC) 22981/26981/National Cancer Institute of Canada (NCIC) CE.3 trial has defined combined chemoradiotherapy to $30 \times 2 = 60$ Gray (Gy) with daily concomitant TMZ at 75 mg/m^2 followed by six cycles of TMZ at 150–200 mg/m^2 on 5/28 days as the standard of care for glioblastoma [26,27▪]. Combined chemoradiotherapy prolonged median overall survival by 2.4 months compared with radiotherapy alone (HR 0.63, 95% CI 0.52–0.75, $P < 0.001$) [26]. However, the trial did not enroll patients older than 70 years and post-hoc analyses suggested decreased efficacy of the addition of TMZ to radiotherapy in patients aged 66–70 years (HR 0.78, 95% CI 0.50–1.25, $P = 0.29$) [28], but the trial was not powered for age stratified efficacy analyses. The efficacy of combined chemoradiotherapy versus radiotherapy alone in elderly patients aged over 65 years with newly diagnosed glioblastoma and good clinical performance is currently being evaluated by an international NCIC/EORTC phase III trial (NCT00482677).

Radiotherapy

The efficacy of postsurgical radiotherapy in elderly patients with glioblastoma or anaplastic astrocytoma was demonstrated by a randomized trial of the Association des Neuro-Oncologues d'Expression Francaise [16]. A total of 81 patients aged 70 years or older with a KPS of at least 70% were randomized to receive best supportive care (BSC) with radiotherapy of contrast-enhancing tumor and a 2 cm margin to

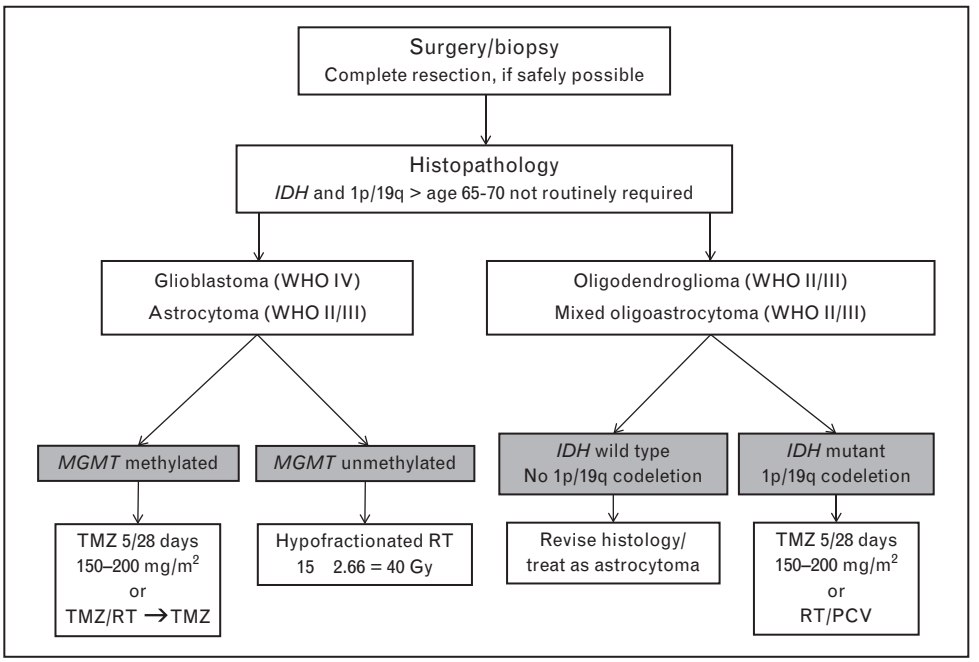

FIGURE 1. Therapeutic approach to diffusely infiltrating gliomas in elderly patients. *IDH,* isocitrate dehydrogenase; *MGMT,* O^6-methylguanine-DNA methyltransferase; PCV, polychemotherapy with procarbazine, CCNU (lomustine) and vincristine; RT, radiotherapy; TMZ, temozolomide. TMZ/RT, $30 \times 2 = 60$ Gray (Gy) with daily concomitant temozolomide at 75 mg/m^2.

50 Gy in fractions of 1.8 Gy, or BSC alone. Radiotherapy prolonged survival approximately two-fold without major impact on quality of life or mental status [16]. A population-based retrospective review of 2836 elderly patients with glioblastoma [median aged 76.9 years (range 71–98)] demonstrated a survival benefit from radiotherapy too, after adjusting for tumor size, tumor location, surgery, and demographics (HR 0.43, 95% CI 0.38–0.49) [29].

Standard radiotherapy for glioblastoma is 54–60 Gy given in 1.8–2 Gy fractions [27▪] and, thus, requires daily traveling during 6 weeks, which may be a particular burden for elderly patients with eminent morbidity. In a randomized trial in patients with glioblastoma aged 60 years or older ($N = 95$), standard radiotherapy of $30 \times 2 = 60$ Gy (mean age 72.4 years) versus hypofractionated radiotherapy of $15 \times 2.66 = 40$ Gy (mean age 71.0 years) yielded similar median survival from the time of diagnosis [6.1 versus 5.9 months, HR 0.90 (95% CI 0.60–1.35), $P = 0.61$] [17]. These results were complemented by subgroup analyses of the phase III Nordic trial, which randomized 291 elderly patients (>60 years) with glioblastoma to three different treatment arms, including TMZ dosed to 150–200 mg/m^2 on 5 of 28 days, standard radiotherapy of $30 \times 2 = 60$ Gy and hypofractionated radiotherapy of $10 \times 3.4 = 34$ Gy [19]. Comparing hypofractionated radiotherapy and standard radiotherapy within the intention to treat (ITT) population among the subgroup of patients aged 70 years or older ($N = 81$), hypofractionated radiotherapy improved overall survival versus standard radiotherapy (7.0 versus 5.2 months, $P = 0.02$), presumably in part because a substantial fraction of patients did not complete the entire course of standard radiotherapy [19]. These trials were not powered to demonstrate the efficacy of both radiotherapy regimens, but, for pragmatic reasons, hypofractionated radiotherapy has become the preferred regimen for elderly patients and patients in poor general condition, across WHO grades [27▪]. Of note, accelerated and lower dose radiotherapy is also an option for the therapy of patients with WHO grade II gliomas [30], but no data particularly evaluating its role in elderly patients are available.

Temozolomide

Among the ITT population of the Nordic trial ($N = 291$), TMZ ($N = 93$) was as efficient as hypofractionated radiotherapy ($N = 98$) [HR 0.82 (96% CI 0.63–1.06)] in a survival model that controlled for age, type of surgery (biopsy versus resection) and WHO performance score [19]. In parallel, the German NOA-08 trial evaluated TMZ as an alternative to radiotherapy in elderly patients with glioblastoma (89%) or anaplastic astrocytoma (11%). The NOA-08 trial enrolled 412 of 584 screened patients aged 65 years or older with a KPS over 60%, of which 373 patients received at least one dose of treatment to be included in efficacy analyses [18]. Radiotherapy

was administered to $30 \times 2 = 60$ Gy and TMZ was administered at a dose-dense schedule of 100 mg/m^2 given on days 1–7 every other week (1 week on/1 week off). In a survival model that controlled for age, histological diagnosis, extent of resection and *MGMT* promoter methylation, the effect of dose-dense TMZ on overall survival was noninferior to standard radiotherapy [HR 1.09 (95 %CI 0.84–1.42)] and overall survival rates after 12 months were 34.4% (95% CI 27.6–41.4) in the TMZ group and 37.4% (95% CI 30.1–44.7) in the radiotherapy group [18]. The comparable results from the Nordic and NOA-08 trials with two different TMZ dosing regimens have yielded standard five of 28 the preferred dosing regimen in elderly patients [27▪], because no additional benefit was noted from dose-intensified TMZ in patients with anaplastic astrocytoma and glioblastoma, whereas toxicity was enhanced [18,31].

In patients aged 70 years or younger, benefit from TMZ was mainly restricted to patients with hypermethylation of the promoter region of *MGMT* [32]. To evaluate whether this accounts for elderly patients too, survival analyses stratified for *MGMT* methylation status were included in the Nordic and NOA-08 trials [18,19]. In both trials *MGMT* methylation predicted benefit from TMZ, and a trend toward inferior survival with TMZ among unmethylated patients was noted (Table 2).

In a retrospective analysis of pooled data from patients assessed within the NOA-04 and NOA-08 trials, and the German Glioma Network, *IDH* mutation assessment refined the predictive role of *MGMT* promoter methylation status for benefit from TMZ in patients with anaplastic gliomas [33]. Further, long-term follow-up data of two phase III trials in patients with anaplastic oligodendroglial gliomas (EORTC 26951 and RTOG 9402) defined 1p/19q codeletion as a strong predictor for benefit from polychemotherapy with procarbazine, lomustine (CCNU) and vincristine (PCV) [10,11]. Yet, assessment of *IDH* mutation status or 1p/19q deletions in elderly patients is not part of clinical routine, because both these markers are rare in elderly patients with diffusely infiltrating gliomas [27▪] and because toxicity from PCV likely limits its utility in elderly patients. Further, TMZ and PCV were similarly active in patients with anaplastic gliomas treated in the NOA-04 trial [12], and therefore, TMZ is advocated as a less toxic alternative to PCV in elderly patients, although a sufficiently powered clinical trial that directly compares PCV versus TMZ in diffusely infiltrating gliomas with 1p/19q codeletion is lacking. In patients with WHO grade II gliomas, benefit from TMZ is predicted by 1p/19q codeletion [34], mutant *IDH* [35], and methylated *MGMT* [36], but the role in elderly patients is elusive

Table 2. Survival of elderly patients treated in the NOA-08 and Nordic trials: stratified by *MGMT* promoter methylation [18,19]

	NOA-08: Age 65 or more, radiotherapy 30×2 Gy versus temozolomide on 7/14 days 100 mg/m^2						Nordic: Age 60 or more, radiotherapy 10×3.4 Gy or 30×2 Gy versus temozolomide on 5/28 days 150–200 mg/m^2					
	Methylated			Unmethylated			Methylated			Unmethylated		
	RT, $N = 42$	TMZ, $N = 31$	P	RT, $N = 59$	TMZ, $N = 77$	P	RT, $N = 63$	TMZ, $N = 28$	P	RT, $N = 68$	TMZ, $N = 44$	P
Median EFS[a]: months (95% CI)	4.6 (4.2–5.0)	8.4 (5.5–11.7)	–	4.6 (3.7–6.3)	3.3 (3.0–3.5)	–	–	–	–	–	–	–
Median OS: months (95% CI)	9.6 (6.4- n.r.)	n.r.	–	10.4 (8.0–11.6)	7.0 (5.7–8.7)	–	8.2 (6.6–9.9)	9.7 (8.0–11.4)	–	7.0 (5.7–8.3)	6.8 (5.9–7.7)	–
HR for EFS[a] (95% CI)[b]	1.0[c]	0.53 (0.33–0.86)	0.01	1.0[c]	1.95 (1.41–2.69)	0.01	–	–	–	–	–	–
HR for OS (95% CI)[b]	1.0[c]	0.69 (0.35–1.16)	0.14	1.0[c]	1.34 (0.92–1.95)	0.13	1.0	0.64 (0.39–1.04)	0.07	1.0	1.16 (0.78–1.72)	0.46

CI, confidence interval; HR, hazard ratio; OS, overall survival; RT, radiotherapy; TMZ, temozolomide.
[a]event-free survival (EFS) or progression-free survival (PFS) were not reported in the Nordic trial.
[b]NOA-08: Cox-regression model correcting for age, extent of resection, histology and *MGMT*; Nordic: No multivariate analyses for EFS or PFS reported; Cox-regression correcting for age, type of surgery (biopsy versus resection), WHO performance score and *MGMT*
[c]methylated and unmethylated tumors were pooled for reference ($N = 178$).

due to the low frequency of these tumors in patients aged over 65 years. Of note, 1p/19q codeletion and mutant *IDH* were not prognostic in a cohort of mostly WHO grade II gliomas that were not treated with radiotherapy or chemotherapy [37,38].

In summary, the Nordic and NOA-08 trials defined a predictive role of *MGMT* promoter methylation for benefit from TMZ, but not radiotherapy, and have thereby defined *MGMT* testing as standard of care in elderly patients with glioblastoma and anaplastic astrocytoma (Fig. 1) [27▪]. The optimal combination of radiotherapy and TMZ for adults of any age with anaplastic gliomas that lack 1p/19q codeletions is currently being evaluated by the EORTC trial CATNON (concurrent and adjuvant temozolomide chemotherapy in non-1p/19q deleted anaplastic glioma) (NCT00626990).

IS ANTIANGIOGENIC TREATMENT AN ALTERNATIVE TO CHEMOTHERAPY OR RADIOTHERAPY?

Two independent placebo-controlled phase III trials [AVAglio (Avastin in glioblastoma) and RTOG 0825] have demonstrated improved progression-free survival, but no overall survival benefit from the addition of the humanized antivascular endothelial growth factor antibody bevacizumab (BEV) to standard combined chemoradiotherapy (radiotherapy/TMZ→TMZ 5/28) in patients with newly diagnosed glioblastoma [39▪▪,40]. The RTOG 0825 trial randomized 637 patients with a median age of 58 years (range: 19–82) in mostly good general condition (KPS 90–100: $N = 378$, 60.9%) [40]. Among 921 patients randomized in the AVAglio trial, the median age was 57 years (range: 18–84), including 369 (40.1%) aged 60 years or older and 630 patients (68.7%) had a KPS of 90 or 100. On univariate analyses, a trend toward improvement of overall survival was noted with increasing age, although not reaching statistical significance (Table 3). Of note, the RTOG 0825 and AVAglio trials were not powered to evaluate the age-stratified efficacy of BEV, but two early uncontrolled trials [41,42] and one retrospective study [43] suggested increased benefit from BEV among elderly patients too, and this appeared to account particularly for patients with poor general condition [42,43]. However, this population was likely underrepresented in the AVAglio and RTOG 0825 trials, because good general condition (KPS>60) was an inclusion criterion in both trials [39▪▪,40]. Currently, the randomized phase II avastin along with radiotherapy in elderly patients with glioblastoma trial is exploring outcomes in patients aged 65 or older with newly diagnosed, *MGMT* unmethylated glioblastoma treated with hypofractionated radiotherapy ($15 \times 2.66 = 40$ Gy) with or without additional BEV (NCT01443676).

Table 3. Age-stratified hazard ratios for overall survival of patients treated within the AVAglio trial [39▪▪]

Age	*N*	HR (95% CI)[a]
<50	229	1.05 (0.76–1.44)
50–59	323	0.90 (0.70–1.16)
60–69	296	0.81 (0.63–1.05)

CI, confidence interval; HR, hazard ratio.
[a]Univariate analyses in patients receiving combined radiochemotherapy with bevacizumab versus placebo.

THERAPEUTIC OPTIONS AT PROGRESSION

To date, no controlled trials specifically evaluating treatment options for elderly patients with recurrent diffusely infiltrating glioma have been conducted. Treatment options include monotherapies or combined regimens containing TMZ, nitrosoureas (in particular CCNU/lomustine), and BEV, dependent on patient and tumor characteristics, pretreatment, availability and local preferences [44]. Based on uncontrolled trials, only patients in good general condition in which gross total resection is safely feasible should be considered for repeat surgery [27▪] and repeat radiotherapy should only be considered in patients with KPS more than 60, small tumors and time of progression over 6 months from surgery when chemotherapy is contraindicated [45]. However, patterns of progression and comorbidities mostly preclude repeat surgery and repeat radiotherapy as an option for elderly patients.

Treatment choice at recurrence is particularly challenging in the majority of elderly patients with *MGMT* unmethylated tumors that were pretreated with hypofractionated radiotherapy, because the efficacy of alkylating chemotherapy is very limited. The Dutch randomized phase II trial BELOB (bevacizumab versus bevacizumab plus lomustine versus lomustine single agent in recurrent glioblastoma) explored the efficacy of lomustine versus BEV versus a combination of both in 153 patients with recurrent glioblastoma at a median age of 57 years [46▪]. Although age-stratified survival analyses were not included in the publication, good treatment tolerability and favorable survival in the combination group versus BEV monotherapy versus lomustine monotherapy (median postrecurrence survival: 12 versus 8 versus 8 months) suggest that the combination of BEV and lomustine may be a valid option for elderly patients with recurrent disease.

Of note, no difference in overall survival was detected in *MGMT* stratified analyses of 43 patients treated with lomustine alone [HR unmethylated versus methylated: 0.89 (95% CI: 0.48–1.64)] and addition of lomustine to BEV in patients with unmethylated *MGMT* increased overall survival rates at 9 months from 12% (95% CI: 3–29) for BEV alone to 58% (95% CI: 37–74) for the combination of BEV and lomustine [46▪], thus suggesting some activity of lomustine in *MGMT* unmethylated glioblastoma. Whether lomustine is active in elderly patients too, remains to be explored. Stratification by age less than 50 versus 50 or more years demonstrated no difference in the efficacy of lomustine in a recent phase III trial for recurrent glioblastoma, which utilized lomustine as standard therapy in 92 patients yielding a 19% progression-free survival rate at 6 months [47]. However, median age or *MGMT* methylation status was not reported and a majority of included patients had a good KPS of 90–100%, thus limiting extrapolations on a frail elderly population.

Hypofractionated radiotherapy at recurrence is the treatment of choice for elderly patients with methylated *MGMT* promoter that received first-line therapy with TMZ [12,18]. TMZ rechallenge may also be considered after a TMZ-free interval in patients that responded to first-line TMZ, that is, essentially patients with *MGMT* methylated tumors [48▪]. Standard dosing at 150–200 mg/m^2 on five of 28 days is preferred [27▪], as dose-intensified TMZ regimens are unlikely to be more active at rechallenge [31,49].

However, randomized trials evaluating treatment options for elderly patients with recurring diffusely infiltrating glioma are required to define a standard of care.

CONCLUSION

Diffusely infiltrating gliomas in elderly patients differ molecularly from their histopathological counterparts in younger patients. Favorable molecular markers including mutant *IDH* and 1p/19q codeletions are rare among elderly patients. Considering molecular similarities, poor prognosis and paucity of available data, we advocate to treat WHO grade II gliomas in elderly patients analogous to WHO grade III/IV gliomas if *IDH* wild-type status is confirmed. *MGMT* promoter methylation predicts benefit from TMZ and should, therefore, be determined in elderly patients with diffusely infiltrating glioma to guide first-line treatment (Fig. 1). Treatment options at recurrence are limited and generally lack evidence from randomized controlled trials. Future clinical trials focusing on the distinct molecular profile of diffusely infiltrating gliomas in the elderly should be conducted for both first-line and second-line treatments.

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- ▪ of special interest
- ▪▪ of outstanding interest

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